



Glucocorticoids, Inhaled Therapeutic Class Review (TCR)

September 7, 2016

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September 2016

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MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Glucocorticoids		
beclomethasone HFA inhalation aerosol (QVAR®) ¹	Teva	<ul style="list-style-type: none"> Maintenance treatment of asthma as prophylactic therapy (see indicated ages below for each product) For asthma patients requiring systemic corticosteroid administration to reduce or eliminate the need for oral systemic corticosteroids Indicated Ages <ul style="list-style-type: none"> QVAR is for use in patients age five 5 years and older Pulmicort Flexhaler is for use in patients age 6 years and older Pulmicort Respules are used in patients age 12 months to 8 years Flovent HFA and Flovent Diskus are for use in patients age 4 years and older Asmanex is for use in patients age 4 years and older Aerospan is for use in patients 6 years and older Alvesco, Arnuity Ellipta, and Asmanex HFA are for adult and adolescent patients 12 years of age and older
budesonide inhalation powder (Pulmicort Flexhaler®) ²	AstraZeneca	
budesonide inhalation suspension (Pulmicort Respules®) ³	AstraZeneca, generic	
ciclesonide inhalation aerosol (Alvesco®) ⁴	Sunovion	
flunisolide HFA (Aerospan®) ⁵	Acton	
fluticasone furoate inhalation powder (Arnuity™ Ellipta®) ⁶	GlaxoSmithKline	
fluticasone propionate inhalation aerosol (Flovent HFA®) ⁷	GlaxoSmithKline	
fluticasone propionate inhalation powder (Flovent Diskus®) ⁸	GlaxoSmithKline	
mometasone furoate inhalation aerosol (Asmanex® HFA) ⁹	Merck	
mometasone furoate inhalation powder (Asmanex® Twisthaler) ¹⁰	Merck	

FDA-Approved Indications (continued)

Glucocorticoid/Bronchodilator Combinations		
Drug	Manufacturer	Indication(s)
budesonide / formoterol inhalation aerosol (Symbicort®) ¹¹	AstraZeneca	<ul style="list-style-type: none"> ▪ Treatment of asthma in patients 12 years of age and older ▪ Maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema
fluticasone furoate / vilanterol (Breo® Ellipta®) ¹²	GlaxoSmithKline	<ul style="list-style-type: none"> ▪ Long-term, once daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema ▪ To reduce exacerbations of COPD in patients with a history of exacerbations ▪ Treatment of asthma in patients 18 years of age and older
fluticasone propionate / salmeterol inhalation aerosol (Advair® HFA) ¹³	GlaxoSmithKline	<ul style="list-style-type: none"> ▪ Treatment of asthma in patients 12 years of age and older
fluticasone propionate / salmeterol inhalation powder (Advair® Diskus) ¹⁴	GlaxoSmithKline	<ul style="list-style-type: none"> ▪ Treatment of asthma in patients 4 years of age and older ▪ Maintenance treatment of airflow obstruction in COPD including chronic bronchitis and emphysema (250 /50 mcg only) ▪ To reduce COPD exacerbations in patients with a history of exacerbations (250 /50 mcg only)
mometasone / formoterol inhalation aerosol (Dulera®) ¹⁵	Merck	<ul style="list-style-type: none"> ▪ Treatment of asthma in patients 12 years of age and older

The manufacturing, sale, and dispensing of chlorofluorocarbon (CFC) containing inhalers has been phased out by the United States (U.S.) Food and Drug Administration (FDA) to comply with the Montreal Protocol.¹⁶ Inhalers utilizing an alternative inhalant technology, as shown above, have emerged to meet the needs of patients left by the void.¹⁷

For asthma therapy, the combination products budesonide/formoterol (Symbicort), fluticasone propionate/salmeterol (Advair Diskus, Advair HFA), mometasone/formoterol (Dulera), and fluticasone furoate/vilanterol (Breo Ellipta) should only be prescribed for patients not adequately controlled on a single-agent long-term asthma control medication, such as an inhaled corticosteroid (ICS), or whose disease severity clearly warrants initiation of treatment with both an ICS and a long-acting beta₂ agonist (LABA). These combination products are not indicated for the relief of acute bronchospasms.

OVERVIEW

Asthma

Prevalence of asthma in the U.S. continues to rise. In 2010, total asthma prevalence was estimated to be 8.4% of the population, or approximately 25.7 million Americans.¹⁸ Further, the National Health Statistics Report shows that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status which can place significant pressure on public health systems.¹⁹ The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.²⁰ In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow

obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli.

Studies have demonstrated the efficacy of inhaled corticosteroids (ICS) in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma.^{21,22,23,24,25} The 2007 National Heart, Lung, and Blood Institute, (NHLBI), and the 2016 Global Initiative for Asthma (GINA) guidelines state that inhaled glucocorticoids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma.^{26,27}

The 2016 GINA guidelines offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects.²⁸ Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes. During this continuous cycle, a stepwise treatment approach is offered to achieve control using the patient's current level of control as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control. A combination ICS/long-acting beta₂-agonist (LABA) product is the preferred step-up treatment for adults and adolescents ≥ 12 years currently on a low dose ICS who continue to have persistent symptoms/exacerbations. The risk of exacerbations can be reduced in adolescents and adults who are using other alternative therapies with treatment of a low dose ICS/formoterol (with beclomethasone or budesonide). For children (6 to 11 years of age) with persistent symptoms, an increased ICS dose is preferred over use of an ICS/LABA agent.

Assessment of Asthma Control from 2016 GINA Guidelines²⁹

Characteristic	Well Controlled (all of the following)	Partly Controlled (any present in past week)	Uncontrolled
A. Assessment of symptom control (preferably over 4 weeks)			
Daytime symptoms more than twice per week	None of these criteria	1 to 2 of these criteria	≥ 3 of these criteria
Limitations of activities			
Nocturnal symptoms/awakening			
Need for reliever/rescue treatment more than twice per week			
B. Risk factors for poor asthma outcomes			
Assess at diagnosis and periodically (and during exacerbations); assess forced expiratory volume in 1 second (FEV ₁) during			
Independent risk factors for exacerbations include (≥ 1 of these risk factors increases risk for exacerbations despite well controlled symptoms):			
<ul style="list-style-type: none">Uncontrolled asthma symptoms, excessive short-acting beta₂-agonist (SABA) use, inadequate ICS, frequent exacerbations in the past, any admission to critical care for asthma, low FEV₁, exposure to cigarette smoke/allergens, major psychological or socioeconomic problems, comorbidities, pregnancy, sputum or blood eosinophilia, intensive care unit (ICU) admission or prior intubation for asthma, and ≥ 1 severe exacerbation in past year			
Fixed air flow limitation risk factors include:			
<ul style="list-style-type: none">Lack of ICS treatment, tobacco/chemical/occupational exposures, and low initial FEV₁			
Risk factors for medication side effects include:			
<ul style="list-style-type: none">Frequent oral corticosteroid use, long-term/high dose ICS, taking P450 inhibitors, and poor inhaler technique			

FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta₂-agonist; SABA = short-acting beta₂-agonist

Stepwise Approach to Asthma Control from 2016 GINA Guidelines³⁰

Adults and Children 6 Years of Age And Older	
Step 1	As-needed reliever medication <ul style="list-style-type: none"> Recommended: SABA Alternative Controller: consider low dose ICS
Step 2	One controller AND an as-needed reliever medication <ul style="list-style-type: none"> Preferred controller: low-dose ICS + SABA Alternative controllers: leukotriene modifier or low dose theophylline*
Step 3	One or 2 controllers and an as-needed reliever medication <ul style="list-style-type: none"> Preferred for adolescents and adults: low-dose ICS AND a LABA as maintenance plus as-needed SABA Preferred for children 6 to 11 years of age: medium dose ICS + as-needed SABA Alternative controllers: medium- or high-dose ICS, OR low-dose ICS + leukotriene modifier, OR Low-dose ICS + sustained-release theophylline*
Step 4	Two or more controllers AND an as-needed reliever medication <ul style="list-style-type: none"> Preferred for adolescents and adults: low dose ICS/formoterol as maintenance + reliever treatment; OR medium-dose ICS + LABA plus as-needed SABA Preferred for children 6 to 11 years of age: referral to expert for assessment and advice Alternative controllers: <ul style="list-style-type: none"> For adults and adolescents: medium- or high-dose ICS, OR low-dose ICS + leukotriene modifier, OR low-dose ICS + sustained release theophylline*, OR tiotropium
Step 5	Higher level of care and/or add-on treatment <ul style="list-style-type: none"> In addition to Step 4 treatment, refer for add-on treatment: Tiotropium, monoclonal antibody treatment (omalizumab [anti-IgE therapy], mepolizumab [anti-IL-5 therapy]), low dose oral corticosteroids, bronchial thermoplasty, or sputum guided therapy

* For children 6 to 11 years of age, theophylline is not recommended.

ICS = inhaled corticosteroid; LABA = long-acting beta₂-agonist; SABA = short-acting beta₂-agonist

The NAEPP Expert Panel Report-3 (EPR-3) report released in 2007 by the NHLBI also recommends a similar classification of asthma severity and control, to guide in the initiation and adjustment of therapy, respectively.³¹ Asthma severity and control are defined in terms of 2 domains, impairment and risk. The distinction between these domains emphasizes the need to consider separately, asthma's effects on quality of life and functional capacity on an ongoing basis (e.g., in the present), along with risks for adverse events, such as exacerbations and progressive loss of pulmonary function.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3³²

Severity of Asthma	Adults and Children ≥ 12 Years	Children from Birth to 4 Years of Age	Children Five to 11 Years of Age
Step 1 Intermittent Asthma	No daily medications needed SABA as needed	No daily medications needed SABA as needed	No daily medications needed SABA as needed
Step 2 Persistent Asthma	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS Alternative: cromolyn or montelukast	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline
Step 3 Persistent Asthma	Low-dose ICS + LABA OR Medium-dose ICS Alternative: Low-dose ICS and 1 of the following: LTRA, theophylline, or zileuton	Medium-dose ICS	Low-dose ICS + LABA OR LTRA OR theophylline OR Medium-dose ICS
Step 4 Persistent Asthma	Medium-dose ICS + LABA Alternative: Medium-dose ICS and 1 of the following: LTRA, theophylline, or zileuton (Zyflo)	Medium-dose ICS + LABA OR montelukast	Medium-dose ICS + LABA Alternative: medium-dose ICS + LTRA OR theophylline
Step 5 Persistent Asthma	High-dose ICS + LABA Consider omalizumab for patients who have allergies	High-dose ICS + LABA OR montelukast	High-dose ICS + LABA Alternative: high-dose ICS + LTRA OR theophylline
Step 6 Persistent Asthma	High-dose ICS + LABA + oral corticosteroid Consider omalizumab for patients who have allergies	High-dose ICS + LABA OR montelukast (Singulair®) + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + LTRA OR theophylline + oral corticosteroids

ICS = inhaled corticosteroid; LABA = long-acting beta₂-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; SABA = short-acting beta₂-agonist

All asthma patients should have a short-acting beta₂-agonist inhaler for use on an as-needed basis.

COPD

The 2016 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) as a preventable and treatable disease in which its pulmonary component is characterized by airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response to noxious particles or gases in the lungs and airways.³³ The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. It is estimated that the number of Americans with a COPD diagnosis exceeds 15 million.³⁴ However, the U.S. Preventive Services Task Force (USPSTF) recommends against routine screening in asymptomatic adults.³⁵

Bronchodilator therapy (e.g., beta₂-agonists, anticholinergics, and methylxanthines) is central to symptom management in COPD, and the inhaled route is preferred. The 2016 GOLD guidelines reference that a subset of LABAs (e.g., formoterol and salmeterol) have demonstrated improvement in FEV₁ and quality of life, as well as decreasing dyspnea and exacerbation and hospitalization rates in COPD patients.³⁶ However, no significant benefit on mortality or the rate of lung function decline has been demonstrated. While most studies indicate that the existing medications for COPD do not modify the long-term decline in lung function, there is limited evidence that regular treatment with LABAs, inhaled corticosteroids (ICS), and their combination can decrease the rate of decline of lung function. Therefore, pharmacotherapy for COPD is mainly used to decrease symptoms and/or complications, potentially improving quality of life. Notably, long-term monotherapy with inhaled corticosteroids at any COPD group (stage) has been shown to be less effective than its use in combination with long-acting beta agonists.

The GOLD Classification of Airflow Limitation, which is divided into 4 Grades (GOLD 1 [mild] to GOLD 4 [very severe]), utilizes these airflow limitation grades in addition to the number of exacerbations/hospitalizations. A COPD exacerbation is defined as an acute event characterized by worsening of the patient's respiratory symptoms that varies from the normal daily variations and requires a change in medication. Hospitalization for a COPD exacerbation signifies a poor diagnosis and increased risk of death. The COPD Assessment Test (CAT, 0-40) or the Clinical COPD Questionnaire (CCQ) is recommended for a comprehensive assessment of symptoms. The Modified British Medical Research Council questionnaire may be used but only assesses breathlessness.

The patient groups are summarized as follows:

- **Patient Group A – Low Risk, Less Symptoms**
GOLD 1 (mild, FEV₁ ≥ 80% predicted) or GOLD 2 (moderate, 50% ≤ FEV₁ < 80% predicted); and/or 0-1 exacerbations per year and no hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1
- **Patient Group B – Low Risk, More Symptoms**
GOLD 1 or GOLD 2; and/or 0-1 exacerbations per year and no hospitalization for exacerbation; and CAT score ≥ 10 or mMRC grade ≥ 2
- **Patient Group C – High Risk, Less Symptoms**
GOLD 3 (severe, 30% ≤ FEV₁ < 50% predicted) or GOLD 4 (very severe, FEV₁ < 30% predicted); and/or ≥ 2 exacerbations per year or ≥ 1 hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1

- **Patient Group D – High Risk, More Symptoms**

GOLD 3 or GOLD 4; and/or ≥ 2 exacerbations per year or ≥ 1 hospitalization for exacerbation; and CAT score ≥ 10 or mMRC grade ≥ 2

For Group A patients, a short-acting inhaled bronchodilator (beta₂-agonist or anticholinergic) used on an as-needed basis is recommended as first choice while a long-acting beta₂-agonist or anticholinergic or the combination of short-acting inhaled beta₂-agonist and short-acting anticholinergic are considered as alternatives.³⁷ For Group B COPD patients, regular use of a long-acting bronchodilator (beta₂-agonist or anticholinergic) is recommended while the combination of a long-acting beta₂-agonist and a long-acting anticholinergic is an alternative treatment. Initial treatment for Group C patients focuses on fixed combinations of inhaled corticosteroid/long-acting bronchodilators (beta₂-agonist or anticholinergic). Alternatively, Group C patients may be initiated on a phosphodiesterase-4 (PDE4) inhibitor plus a long-acting bronchodilator (beta₂-agonist or anticholinergic) or a long-acting anticholinergic plus a long-acting beta₂-agonist. Group D patients may utilize the same initial therapeutic plan as those in Group C with a goal of reducing exacerbations. There is some evidence for use of triple therapy for Group D patients: inhaled corticosteroid plus 2 long-acting inhaled bronchodilators. The 2016 update states that withdrawal of ICS in stable COPD patients with a low risk of exacerbation may be safely accomplished, provided that the patient remains on maintenance treatment with a long-acting bronchodilator. In addition, it states that an ICS/LABA combination product administered once daily does not clinically differ in efficacy compared to a twice-daily regimen.

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) COPD guidelines include a fifth category or group, “At Risk”, which is based on the presence (FEV₁/FVC ratio < 0.7 and FEV₁ $\geq 50\%$ predicted) or absence (FEV₁/FVC ratio ≥ 0.7) of mild to moderate airflow obstruction in asymptomatic individuals and risk factors including smoking or exposure to pollutants with cough, sputum, or dyspnea, or a family history of respiratory disease.³⁸ However, these guidelines do not support routine treatment with bronchodilators in the asymptomatic “At Risk” group as there are limited data to support that such treatment influences the trajectory of the disease. Albeit a weak recommendation, the 2011 guidelines do suggest that stable, symptomatic COPD patients with an FEV₁ between 60% and 80% may be treated with inhaled bronchodilators (anticholinergics or long-acting beta₂-agonists). For stable, symptomatic patients with an FEV₁ less than 60%, monotherapy with an inhaled bronchodilator is strongly recommended. The type of bronchodilator may be selected based on patient parameters, cost, and adverse effect profile. Combination therapy with an inhaled long-acting beta₂-agonist, inhaled long-acting anticholinergic, or inhaled corticosteroid may be used in lieu of monotherapy for patients with FEV₁ less than 60%; however, the group has offered this as a weak recommendation due to the moderate quality of evidence. Further, the guidelines suggest there is no clear outline for which patients would benefit the most from combination therapy over monotherapy.

A 2015 joint guideline from for the American College of Chest Physicians and the Canadian Thoracic Society also recommends treatments based on data from published trials on decreased acute exacerbations of COPD.³⁹ They recommend the use of long-acting beta₂-agonists (Grade 1B) and long-acting antimuscarinics (Grade 1A) over no treatment in patients with moderate to severe COPD, stating that long-acting antimuscarinics are preferred (Grade 1C). Likewise, they recommend short-acting antimuscarinic agents for monotherapy over short-acting beta₂-agonists (Grade 2C) but further state that the combination is also preferred over short-acting beta₂-agonist monotherapy (Grade 2B). However, long-acting beta₂-agonist or anticholinergic monotherapy is preferred over short-acting antimuscarinic

monotherapy (Grade 2C and Grade 1A, respectively). Long-acting combination therapy, including inhaled corticosteroids, is also preferred over monotherapy in patients with severe COPD (range, Grade 1B to 1C). Overall, recommendations in these guidelines are based on qualifying patients as those with mild, moderate, or severe COPD rather than GOLD classification or high-risk.

Direct head-to-head studies of combination ICS/LABA and ICS/long-acting anticholinergics are widely absent making comparison and differentiation difficult.⁴⁰ A Cochrane Review suggests no significant difference in mortality or lung function (FEV₁) between tiotropium, a long-acting anticholinergic agent, and LABAs; however, statistically significant differences in the number of patients experiencing 1 or more exacerbations were seen in favor of tiotropium, particularly when compared against salmeterol (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.79 to 0.93).⁴¹ Tiotropium and related anticholinergic products are reviewed under a separate Therapeutic Class Review.

PHARMACOLOGY^{42,43,44,45,46,47,48,49,50,51}

Corticosteroids suppress the cytokine generation, recruitment of airway eosinophils, and release of inflammatory mediators. These agents thereby block late-phase reaction to allergens, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.⁵² Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids (ICS) are preferred for asthma.

Advair is a combination product containing a long-acting beta₂-agonist (LABA), salmeterol DPI (Serevent) and a corticosteroid, fluticasone (as propionate). Breo Ellipta also contains the ICS fluticasone (as furoate), as well as the LABA vilanterol. Symbicort is a combination product containing a LABA, formoterol, and an ICS, budesonide. Dulera is a combination product containing the LABA, formoterol and the ICS, mometasone. Formoterol, vilanterol, and salmeterol selectively bind to the beta₂-receptors in the bronchial smooth muscle, leading to bronchial relaxation and a decrease in the release of mediators of immediate hypersensitivity from mast cells.

Delivery and Deposition

The selection of a delivery system and the patients' ability to use the device properly are critical factors in determining clinical success of inhaled corticosteroid therapy. Delivery systems can significantly affect both topical and systemic activity of ICS.^{53,54}

Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution, for which the user has to press down on the metal canister to release the medicine and then inhale. MDIs deliver approximately 15% to 35% of the administered dose to the lungs. Spacer chambers can be attached to MDIs to make them easier to use by people who find it hard to coordinate the press-and-breathe action. When using the spacer, the user can take several breaths to inhale the medicine, which is held in the chamber, so that it is more likely that the proper amount of medicine will reach the airways. MDIs with CFC propellants are no longer manufactured.

Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder when the user breathes in. Although DPIs minimize the potential difficulties in coordinating the press-and-breathe action of the MDI, these delivery systems tend to result in more dosage variations than MDIs at low inspiratory flow rates (less than 20 L/min).

Nebulizer therapy is not the recommended form of administration for most patients.⁵⁵ It is considered inferior to an MDI with spacer because of the inconvenience, higher risk of side effects, and potentially

higher cost. It may be considered an alternative in cases where patients lack the coordination to use the MDI with spacer, particularly in the very young and the very old.

PHARMACOKINETICS^{56,57,58,59,60,61,62,63,64,65,66,67,68,69,70}

Several comparative studies have demonstrated that, when given in equipotent anti-inflammatory doses, fluticasone propionate (Flovent) and budesonide (Pulmicort) have less systemic effect, as measured by plasma cortisol, than the other agents.^{71,72,73,74,75} There is, however, considerable intersubject variability in the rate of absorption of these agents from the lungs.⁷⁶

The NAEPP guidelines provide information regarding the relative potencies and dosages of each of the available agents, as seen in the table below.⁷⁷ It should be noted that these are not the FDA-approved doses, but rather those doses shown to be clinically effective and recommended by the NHLBI. Mometasone (Asmanex) for pediatrics and ciclesonide (Alvesco) were approved after the release of the 2007 NAEPP report and are therefore not contained in the following comparative chart. However, since 2008, mometasone and ciclesonide have been included in the GINA guidelines. Flunisolide (Aerospan) became commercially available in 2014 and is not addressed in the 2016 GINA guidelines.

NAEPP Expert Panel Report-3 Estimated Comparative Daily Dosages for Inhaled Corticosteroids (mcg/day)⁷⁸

Drug	Adults and Children ≥ 12 Years of Age			Children (5 to 11 Years of Age)		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
beclomethasone HFA inhalation aerosol (QVAR)	80–240	240–480	> 480	80–160	> 160–320	> 320
budesonide inhalation powder (Pulmicort)	180–600	> 600–1,200	> 1,200	180–400	> 400–800	> 800
budesonide inhaled suspension (Pulmicort Respules)	n/a	n/a	n/a	0.5 mg (ages 5 to 8 years)	1 mg (ages 5 to 8 years)	2 mg (ages 5 to 8 years)
fluticasone propionate HFA inhalation aerosol (Flovent HFA)	88–264	264–440	> 440	88–176	> 176–352	> 352
mometasone inhalation powder (Asmanex Twisthaler)	200	400	> 400	n/a	n/a	n/a

n/a= not available

Most of the agents in this class are recommended for twice daily use. The exceptions to this are mometasone (Asmanex DPI), fluticasone furoate/vilanterol (Breo Ellipta), and fluticasone furoate inhalation powder (Arnuity Ellipta), which can be dosed once daily.

2016 GINA Guidelines for Equipotent Dosages of Inhaled Corticosteroids (mcg/day)⁷⁹

Drug	Adults			Children		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
beclomethasone HFA inhalation aerosol (QVAR)	100–200	> 200–400	> 400	100–200	> 200–400	> 400
budesonide inhalation powder (Pulmicort)	200–400	> 400–800	> 800	100–200	> 200–400	> 400
budesonide respules (Pulmicort Respules)	n/a	n/a	n/a	250–500	> 500–1,000	> 1,000
ciclesonide inhalation aerosol (Alvesco)	80–160	> 160–320	> 320	80–160	> 160–320	> 320
fluticasone furoate inhalation powder (Arnuity Ellipta)	100	n/a	200	n/a	n/a	n/a
fluticasone propionate inhalation aerosol (Flovent)	100–250	> 250–500	> 500	100–200	> 200–500	> 500
fluticasone propionate inhalation powder (Flovent Diskus)	100–250	> 250–500	> 500	100–200	> 200–400	> 400
mometasone inhalation powder (Asmanex)	110–220	≥ 220–440	≥ 800	110	≥ 220– < 440	≥ 440

Onset of Action

Drug	Onset of action	Maximum benefit
Glucocorticoids		
beclomethasone HFA inhalation aerosol (QVAR)	1 to 2 weeks	3 to 4 weeks
budesonide inhalation powder (Pulmicort Flexhaler)	24 hours	1 to 2 weeks
budesonide suspension (Pulmicort Respules)	2 to 8 days	4 to 6 weeks
ciclesonide inhalation aerosol (Alvesco)	--	4 weeks or longer
flunisolide HFA inhalation aerosol (Aerospan)	--	3 to 4 weeks
fluticasone furoate inhalation powder (Arnuity Ellipta)	variable	2 weeks or longer
fluticasone propionate inhalation aerosol (Flovent HFA)	24 hours – variable time to onset	1 to 2 weeks or longer
fluticasone propionate powder for inhalation (Flovent Diskus)	24 hours – variable time to onset	1 to 2 weeks or longer
mometasone furoate inhalation aerosol (Asmanex HFA)	variable	1 week or longer
mometasone furoate inhalation powder (Asmanex)	1 to 2.5 hours	1 to 2 weeks or longer
Glucocorticoids/Bronchodilator combinations		
budesonide/formoterol inhalation aerosol (Symbicort)	15 minutes for asthma; 5 minutes for COPD	2 weeks or longer
fluticasone furoate/vilanterol (Breo Ellipta)	16 minutes	nr
fluticasone propionate/salmeterol inhalation powder (Advair Diskus)	30–60 minutes	1 week or longer
fluticasone propionate/salmeterol inhalation aerosol (Advair HFA)	30–60 minutes	1 week or longer
mometasone/formoterol inhalation aerosol (Dulera)	variable	1 week or longer

CONTRAINDICATIONS/WARNINGS^{80,81,82,83,84,85,86,87,88,89,90}

All of these agents are contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

A boxed warning exists for all long-acting beta₂ agonists (LABAs; e.g., salmeterol and formoterol), as well as all combination products that contain them [e.g., fluticasone propionate/salmeterol (Advair HFA, Advair Diskus), budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), fluticasone furoate/vilanterol (Breo Ellipta)]. For Advair Diskus, Advair HFA, Symbicort, Dulera, and Breo Ellipta, the boxed warnings warn of the following:

- LABAs increase the risk of asthma-related deaths.
- Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.
- These findings are considered a class effect of all LABAs.

- When treating patients with asthma these agents should be prescribed for only those patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid (ICS), or whose disease severity clearly warrants initiation of treatment with both an ICS and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Advair, Symbicort, Dulera, or Breo Ellipta) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use these agents for patients whose asthma is adequately controlled on low or medium dose ICS.

The inhalation powder formulations of fluticasone furoate (Arnuity Ellipta), fluticasone propionate (Flovent Diskus), fluticasone furoate/vilanterol (Breo Ellipta) and fluticasone propionate/salmeterol (Advair Diskus) are contraindicated in patients who have a severe hypersensitivity to milk proteins as these products contain milk proteins.

Decreased bone mineral density (BMD) has been observed with the long-term administration of products containing inhaled glucocorticoids.⁹¹ The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated according to the current standards of care.

There have been postmarketing reports of esophageal candidiasis for fluticasone propionate (Flovent Diskus, Flovent HFA).

Risk Evaluation and Mitigation Strategy

The products that contain a LABA (Advair Diskus, Advair HFA, Breo Ellipta, Dulera, and Symbicort) do not have REMS requirements issued by the FDA; however, a medication guide has been included in the product labeling.

DRUG INTERACTIONS^{92,93,94,95,96,97,98,99,100}

The main route of metabolism for many corticosteroids is via the cytochrome P450 isoenzyme 3A4. Inhibitors of CYP3A4 (ritonavir, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentration of inhaled corticosteroids (ICS). Fluticasone propionate (Flovent) use in combination with ritonavir has been associated with systemic corticosteroid effects, such as Cushing's syndrome and adrenal suppression.

Products containing salmeterol, formoterol, or vilanterol (Advair Diskus, Advair HFA, Breo Ellipta, Dulera, Symbicort) should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the action of the long-acting beta₂ agonist (LABA), on the cardiovascular system may be potentiated by these agents. Concomitant treatment with xanthine derivatives or diuretics may potentiate any hypokalemic effect of the LABA. Beta-blockers and diuretics should be used caution with drugs containing a LABA. Beta-blockers may interfere with the bronchodilatory effect of the LABA resulting in bronchospasm. Electrolyte abnormalities, such as hypokalemia, exacerbated by diuretics may be enhanced by concomitant beta-agonist usage.

ADVERSE EFFECTS^{101,102,103,104,105,106,107,108,109,110,111,112,113,114,115}

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	Upper respiratory infection
Glucocorticoids						
beclomethasone HFA inhalation aerosol (QVAR)	1–3	12	1	0	8	9
budesonide inhalation powder (Pulmicort Flexhaler)	nr	nr	1.8	1.3	2.7	2.2
budesonide suspension (Pulmicort Respules)	5–9	> 3	nr	nr	> 3	34–38
ciclesonide inhalation aerosol (Alvesco)	< 1	4.9–11	< 1	< 1	7–10.5	4.1–8.7
flunisolide HFA inhalation aerosol (Aerospan)	1.8–8.5	8.8–13.8	nr	nr	16.6–17.5	nr
fluticasone furoate inhalation powder (Arnuity Ellipta)	0–3	10–13	reported	< 1–3	3–6	2–6
fluticasone propionate powder for inhalation (Flovent Diskus)	1–5	2–14	1–8	< 1–9	3–22	14–21
fluticasone propionate inhalation aerosol (Flovent HFA)	4–6	5–11	reported	2–5	1–3	16–18
mometasone furoate inhalation aerosol (Asmanex HFA)	nr	3–5	reported	reported	5–8	nr
mometasone furoate inhalation powder (Asmanex)	nr	20–22	1–3	4–6	8–13	8–15
Glucocorticoid/Bronchodilator Combinations						
budesonide/formoterol inhalation aerosol (Symbicort)	reported	6.5–11.3	reported	1.4–6	7.3–10.5	3.5–10.5
fluticasone propionate/salmeterol inhalation powder (Advair Diskus)	3–6	12–13	4–6	1–4	10–13	21–27
fluticasone propionate/salmeterol inhalation aerosol (Advair HFA)	reported	21	5	1–3	nr	16
fluticasone furoate/vilanterol (Breo Ellipta)	nr	5–7	nr	2–5	9–10	7 (nr in asthma)
mometasone/ formoterol inhalation aerosol (Dulera)	nr	2.0–4.5	nr	0.7–0.8	4.7	nr

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

In 2010, the FDA issued new recommendations on the safe use of LABAs in the treatment of asthma, which also applied to the combination products of budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone propionate/salmeterol (Advair Diskus, Advair HFA).¹¹⁶ The FDA recommends against the use of LABAs without the use of an asthma controller medication, such as an inhaled corticosteroid (ICS). Also, LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. They should be used long-term only in patients whose asthma is not adequately controlled on asthma controller medications. Additionally, in April 2011, to further evaluate the safety of LABAs when used in combination with ICS for the treatment of asthma, the FDA is requiring the manufacturers of LABAs to conduct 5 randomized, double-blind, controlled clinical trials to further evaluate the safety of LABAs when used in combination with ICS in comparison to ICS alone. These clinical trials began in 2011 and the FDA expects to receive results in 2017.¹¹⁷

SPECIAL POPULATIONS^{118,119,120,121,122,123,124,125,126,127,128,129,130}

Pediatrics

Safety and effectiveness of budesonide/formoterol (Symbicort), ciclesonide (Alvesco), fluticasone furoate (Arnuity Ellipta), fluticasone propionate/salmeterol (Advair HFA), mometasone furoate (Asmanex HFA), and mometasone/formoterol (Dulera) in children under age 12 have not been proven. Safety and effectiveness of budesonide (Pulmicort Flexhaler) in children less than 6 years have not been established. Beclomethasone (QVAR) in children less than 5 years has not been proven safe or effective. Flunisolide (Aerospan) in children less than 6 years has not been proven safe or effective. Fluticasone propionate/salmeterol (Advair Diskus) and fluticasone propionate (Flovent HFA, Flovent Diskus) in children younger than 4 years have not been proven safe or effective. Mometasone (Asmanex) is approved for maintenance treatment of asthma as prophylactic therapy for children age 4 years and older. The safety and efficacy of fluticasone furoate/vilanterol (Breo Ellipta) has not been established in pediatric patients.

Budesonide respules (Pulmicort Respules) are indicated specifically for children between 12 months and 8 years of age.

A Cochrane review of 33 randomized controlled trials (RCTs) assessing the efficacy and safety of adding a LABA to an ICS in 6,381 children and adolescents with asthma found that the LABA addition did not result in a significant reduction in exacerbation rate requiring systemic corticosteroids (risk ratio [RR], 0.95; 95% CI, 0.7 to 1.28; 12 RCTs; 1,669 children; moderate quality evidence) but did find superiority in improving lung function compared to the same or higher doses of ICS monotherapy (FEV₁, morning PEF, reduction in use of daytime rescue inhalations, and reduction in use of nighttime rescue inhalations).¹³¹ No significant differences were found in adverse effects; however, there was greater growth in the ICS/LABA group compared to a higher ICS monotherapy dose.

Pregnancy

All products assigned a Pregnancy Category in this class are Pregnancy Category C except budesonide (Pulmicort), which is Pregnancy Category B.

Fluticasone products (Flovent HFA, Flovent Diskus) and mometasone (Asmanex HFA) and mometasone/formoterol (Dulera) are not assigned a Pregnancy Category based on updated prescribing information complying with the Pregnancy and Lactation Labeling Rule. There are no randomized

clinical studies of these agents in pregnant women; thus, a risk versus benefit assessment should be conducted prior to using these agents in pregnant women.

Hepatic Impairment

Close monitoring of patients using fluticasone propionate/salmeterol (Advair) or budesonide/formoterol (Symbicort) who have hepatic impairment is recommended due to accumulation of both active ingredients. Caution is advised when fluticasone furoate/vilanterol (Breo Ellipta) and fluticasone furoate (Arnuity Ellipta) are administered to patients with moderate to severe hepatic impairment. Formal studies of fluticasone propionate (Flovent Diskus, Flovent HFA) have not been performed in subjects with hepatic impairment; however, since it is predominantly metabolized by the liver hepatic impairment may lead to increased plasma concentrations. Thus, caution should be used in patients with hepatic impairment. In contrast vilanterol is unaffected by hepatic impairment. Patients with hepatic impairment should be monitored for corticosteroid-related side effects.

DOSAGES^{132,133,134,135,136,137,138,139,140,141,142,143,144,145,146}

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
beclomethasone HFA inhalation aerosol (QVAR)	40 to 80 mcg twice daily (previous bronchodilator use alone); 40 to 160 mcg twice daily (previous inhaled corticosteroid therapy)	320 mcg twice daily	Age 5 to 11 years: 40 mcg twice daily	Age 5 to 11 years: 80 mcg twice daily	40 and 80 mcg MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths
budesonide inhalation powder (Pulmicort Flexhaler)	360 mcg twice daily	720 mcg twice daily	Age 6 to 17 years: 180 mcg twice daily	Age 6 to 17 years: 360 mcg twice daily	90 and 180 mcg DPI (60 and 120 actuations per canister, respectively) Dose counter available for all strengths Breath activated device
budesonide inhalation suspension (Pulmicort Respules)	--	--	Age 12 months to 8 years: Prior bronchodilator alone: 500 mcg once daily or 250 mcg twice daily Prior ICS: 500 mcg once daily or 250 to 500 mcg twice daily Prior oral glucocorticoid: 500 mcg twice daily or 1,000 mcg once daily	--	250, 500, and 1,000 mcg per 2 mL Respules via jet nebulizer

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
ciclesonide inhalation aerosol (Alvesco)	80 mcg twice daily (patients who received bronchodilator alone)	160 mcg twice daily	Age 12 years and older: 80 mcg twice daily (patients who received bronchodilator alone)	Age 12 years and older: 160 mcg twice daily	80 and 160 mcg MDI with HFA propellant (60 actuations per canister) Dose counter available for all strengths
	80 mcg twice daily (patients who received inhaled corticosteroid)	320 mcg twice daily	Age 12 years and older: 80 mcg twice daily (patients who received inhaled corticosteroid)	Age 12 years and older: 320 mcg twice daily	
	320 mcg twice daily (patients who received oral corticosteroids)	320 mcg twice daily	Age 12 years and older: 120 mcg twice daily (patients who received oral corticosteroid)	Age 12 years and older: 320 mcg twice daily	
flunisolide HFA inhalation aerosol (Aerospan)	160 mcg twice daily	320 mcg twice daily*	80 mcg twice daily	160 mcg twice daily*	80 mcg MDI with HFA propellant (8.9 g canister has 120 actuations per canister)
fluticasone furoate inhalation powder (Arnuity Ellipta)	One Inhalation of 100 mcg or 200 mcg once daily (starting dose based on prior asthma therapy and disease severity)	200 mcg daily	Age 12 years and older: 1 Inhalation of 100 mcg or 200 mcg once daily	Age 12 years and older: 200 mcg daily	100 and 200 mcg blister strip of powder for inhalation (each package contains 30 blisters) Breath activated device

* Higher doses have not been studied.

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
fluticasone propionate inhalation aerosol (Flovent HFA)	88 mcg twice daily (patients who received bronchodilator alone); 88–220 mcg twice daily (patients who used ICS); 440 mcg twice daily (patients who used oral corticosteroids)	440 mcg twice daily 440 mcg twice daily 880 mcg twice daily	Age 4 to 11 years: 88 mcg twice daily	Age 4 to 11 years: 88 mcg twice daily	44, 110, 220 mcg MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths
fluticasone propionate inhalation powder (Flovent Diskus)	100 mcg twice daily (patients who received bronchodilators alone)	500 mcg twice daily	Age 4 to 11 years: 50 mcg twice daily (when prior therapy is with bronchodilator alone or inhaled corticosteroid)	Age 4 to 11 years: 100 mcg twice daily	50, 100, and 250 mcg blister units (60 blisters per pack) Dose counter available for all strengths Breath activated device
	100–250 mcg twice daily (patients who used ICS)	500 mcg twice daily			
	500–1,000 mcg twice daily (patients who used oral corticosteroids)	1,000 mcg twice daily			
mometasone furoate inhalation aerosol (Asmanex HFA)	Based on prior asthma therapy: 2 inhalations of 100 mcg or 200 mcg twice daily	400 mcg twice daily	Age 12 years and older: 2 inhalations of 100 mcg or 200 mcg twice daily	Age 12 years and older: 400 mcg twice daily	100 and 200 mcg pressurized metered dose inhalers (120 actuations per unit)

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
mometasone furoate inhalation powder (Asmanex Twisthaler)	220 mcg daily in evening (if on bronchodilator alone or inhaled corticosteroid) or 440 mcg twice daily (if on oral corticosteroid)	440 mcg daily (single or divided doses) or 880 mcg daily	Age 12 years and older: 220 mcg daily in evening (if on bronchodilator alone or inhaled steroid) or 440 mcg twice daily (if on oral corticosteroid) Age 4 to 11 years of age: 110 mcg once daily in the evening	Age 12 years and older: 440 mcg daily (single or divided doses) or 880 mcg daily Age 4 to 11 years of age: 110 mcg once daily in the evening	110 and 220 mcg DPI (110 mcg: 30 actuations per unit; 220 mcg: 30, 60, or 120 actuations per unit) Dose counter available for all strengths Breath activated device
Glucocorticoid/Bronchodilator Combinations					
budesonide/formoterol inhalation aerosol (Symbicort)	2 inhalations twice daily of 80/4.5 mcg or 160/4.5 mcg	2 inhalations twice daily of 160/4.5 mcg	Age 12 years and older: 2 inhalations twice daily of 80/4.5 mcg or 160/4.5 mcg	Age 12 years and older: 2 inhalations twice daily of 160/4.5 mcg	80/4.5 and 160/4.5 mcg per actuation MDI with HFA propellant (60 or 120 actuations per canister) Dose counter available for all strengths
fluticasone furoate/vilanterol inhalation powder (Breo Ellipta) The recommended starting dosages for asthma are based on prior asthma therapy (ICS)	Asthma: Low-to mid-dose ICS: 1 inhalation of 100/25 mcg once daily Mid- to high-dose ICS: 1 inhalation of 200/ 25 mcg once daily COPD: 1 inhalation of 100/25 mcg once daily	Asthma: 1 inhalation of 200/25 mcg once daily COPD: 1 inhalation of 100/25 mcg once daily	--	--	100/25 and 200/25 mcg per inhalation (60 actuations per unit) Dose counter available Breath activated device

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoid/Bronchodilator Combinations					
fluticasone propionate/salmeterol inhalation aerosol (Advair HFA)	2 inhalations of 45/21 mcg twice daily or 115/21 mcg twice daily or 230/21 mcg twice daily	2 inhalations of 230/21 mcg twice daily	Age 12 years and older: 2 inhalations of 45/21 mcg twice daily or 115/21 mcg twice daily or 230/21 mcg twice daily	Age 12 years and older: 2 inhalations of 230/21 mcg twice daily	45/21, 115/21, and 230/21 mcg per actuation MDI with HFA propellant (60 or 120 actuations per canister) Dose counter available for all strengths
fluticasone propionate/salmeterol inhalation powder (Advair Diskus)	Asthma: 100 50 mcg twice daily to 500/50 mcg twice daily Maintenance treatment of COPD: 1 inhalation twice daily of 250/50 mcg	Asthma: 500/50 mcg twice daily	Age 4 to 11 years: 100/50 mcg twice daily Age 12 years and older: 1 inhalation twice daily of 100/50, 250/50, or 500/50 mcg	--	100/50, 250/50, and 500/50 mcg per actuation Diskus DPI (60 blisters/actuations per unit) Dose counter available for all strengths Breath activated device
mometasone/formoterol inhalation aerosol (Dulera) The recommended starting dosages are based on prior asthma therapy	For medium dose ICS: 2 inhalations of 100/5 mcg twice daily For high dose ICS: 2 inhalations of 200/5 mcg twice daily	Dose ICS: 2 inhalations of 100/5 mcg twice daily For high dose ICS: 2 inhalations of 200/5 mcg twice daily	Age 12 years and older: For medium dose ICS: 2 inhalations of 100/5 mcg twice daily For high dose ICS: 2 inhalations of 200/5 mcg twice daily	Age 12 years and older: For medium dose ICS: 2 inhalations of 100/5 mcg twice daily For high dose ICS: 2 inhalations of 200/5 mcg twice daily	100/5 and 200/5 mcg per actuation (120 actuations per unit) Dose counter available for all strengths

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

beclomethasone MDI (QVAR) versus placebo

The Treating Children to Prevent Exacerbations of Asthma (TREXA) study was a multi-center, 44-week, randomized, double-blind, placebo-controlled trial conducted in 288 children and adolescents with mild persistent asthma aged 6 to 18 years to evaluate the impact and severity of asthma exacerbations in patients who are receiving various combinations of medications for daily and rescue use.¹⁴⁷ Patients were randomly assigned to 1 of 4 treatment groups: twice daily beclomethasone with beclomethasone plus albuterol as rescue (combined group, n=71); twice daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group, n=72); twice daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group, n=71); and twice daily placebo with placebo plus albuterol as rescue (placebo group, n=74). Twice daily beclomethasone treatment was 1 puff of beclomethasone (40 mcg per puff) or placebo given in the morning and evening. Rescue beclomethasone treatment was 2 puffs of beclomethasone or placebo for each 2 puffs of albuterol (180 mcg) needed for symptom relief. The primary outcome was time to first exacerbation that required oral corticosteroids. A secondary outcome measured linear growth. Analysis was by intention to treat. Compared with the placebo group (49%; 95% CI, 37 to 61), the frequency of exacerbations was lower in the daily (28%; 95% CI, 18 to 40; p=0.03), combined (31%; 95% CI, 21 to 43; p=0.07), and rescue (35%; 95% CI, 24 to 47; p=0.07) groups. Frequency of treatment failure was 23% (95% CI, 14 to 43) in the placebo group, compared with 5.6% (95% CI, 1.6 to 14) in the combined (p=0.012), 2.8% (95% CI, 0 to 10) in the daily (p=0.009), and 8.5% (95% CI, 2 to 15) in the rescue (p=0.024) groups. Compared with the placebo group, linear growth was 1.1 cm (standard deviation [SD], 0.3) less in the combined and daily arms (p<0.0001), but not the rescue group (p=0.26). Only 2 individuals had severe adverse events; 1 in the daily beclomethasone group had viral meningitis and 1 in the combined group had bronchitis. The authors concluded that children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations is daily inhaled corticosteroids. ICS as rescue medication with albuterol might be an effective step-down strategy for children with well controlled, mild asthma because it is more effective at reducing exacerbations than

is use of rescue albuterol alone. Use of daily ICS treatment and related side-effects, such as growth impairment, can therefore be avoided. This study was funded by the National Heart, Lung and Blood Institute.

budesonide/formoterol MDI (Symbicort) versus budesonide DPI (Pulmicort)

A double-blind, randomized, 12-week study conducted in 619 patients ages 12 and older with mild to moderate asthma to evaluate the efficacy and tolerability of once daily budesonide/formoterol versus once daily budesonide in patients stable with twice daily budesonide/formoterol.¹⁴⁸ After an initial 4 to 5 weeks of 2 inhalations twice daily budesonide/formoterol 80/4.5 mcg (daily dose of 320/18 mcg), stable patients were randomized to 1 of 4 treatment groups. These groups included: 2 inhalations of twice daily of budesonide/formoterol 80/4.5 mcg (daily dose 320/18 mcg); 2 inhalations once daily in the evening of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg (daily dose of 320/9 mcg or 160/4.5 mcg); or 2 inhalations once daily of budesonide 160 mcg (daily dose of 320 mcg). All budesonide/formoterol groups maintained significantly more favorable evening pre-dose forced expiratory volume in 1 second (FEV₁), morning peak expiratory flow (PEF), daytime/nighttime asthma symptoms, nighttime rescue medication use, and rescue medication-free days versus budesonide. Variables evaluated during the end of the once daily dosing interval included evening pre-dose FEV₁, evening PEF, daytime asthma symptoms, and daytime rescue medication use. They significantly favored twice daily budesonide/formoterol versus all treatments. Twice daily budesonide/formoterol demonstrated significantly more favorable results for symptom-free and asthma control days versus all treatments and awakening-free nights versus budesonide. Asthma Quality of Life Questionnaire and Asthma Control Questionnaire results significantly favored twice-daily budesonide/formoterol versus budesonide ($p \leq 0.018$). All treatments were well tolerated.

A double-blind, randomized, 12-week multicenter study was conducted in 521 patients ages 6 to 15 years with mild/moderate persistent asthma to assess the efficacy and tolerability of once daily budesonide/formoterol metered-dose inhaler (MDI) versus budesonide MDI (primary) and twice daily budesonide/formoterol MDI (secondary) in children/adolescents with asthma who have been stabilized with twice daily budesonide/formoterol MDI.¹⁴⁹ Patients had been stabilized during a 4 to 5 week run-in with 2 inhalations twice daily of budesonide/formoterol 40/4.5 mcg inhalations (160/18 mcg daily). These patients were randomized to either continue on the stabilization regimen, to receive a reduced dose of 2 inhalations once every evening of daily budesonide/formoterol 80/4.5 mcg (160/9 mcg daily), or 2 inhalations once every evening of budesonide 80 mcg (160 mcg daily). The once or twice daily regimens of budesonide/formoterol were more effective than budesonide for evening PEF (primary variable) at the end of the 24 hour once daily dosing interval ($p \leq 0.027$). Twice daily budesonide/formoterol demonstrated better efficacy versus once daily treatments for evening pre-dose FEV₁ ($p \leq 0.011$), versus budesonide for daytime/nighttime rescue medication ($p \leq 0.023$), and versus once daily budesonide/formoterol for daytime rescue medication (last 12 hours of once daily dosing) ($p = 0.032$). There were no significant between-group differences for daytime/nighttime asthma symptoms, nighttime awakenings attributed to asthma, or health-related quality of life. Fewer patients experienced asthma worsening based on predefined criteria with twice daily budesonide/formoterol (8.2%) versus once daily budesonide (15.5%) ($p = 0.036$) or once daily budesonide/formoterol (19.6%) ($p = 0.002$). All treatments were well tolerated.

budesonide/formoterol MDI (Symbicort) versus budesonide DPI (Pulmicort) versus formoterol MDI (Foradil) versus budesonide (Pulmicort) + formoterol (Foradil) versus placebo

A 12-week, randomized, double-blind, double-dummy, placebo-controlled study was conducted to compare the efficacy and safety of budesonide/formoterol to each of its individual ingredients [budesonide, formoterol, or budesonide + formoterol] as well as to placebo.¹⁵⁰ Five hundred ninety-six patients ages 12 years and older with moderate to severe persistent asthma and previously receiving an ICS were placed on budesonide 160 mcg twice daily. After 2 weeks, they were randomized to budesonide/formoterol 160/4.5 mcg twice daily; budesonide 160 mcg twice daily + formoterol 4.5 mcg twice daily; budesonide 160 mcg twice daily; formoterol 4.5 mcg twice daily; or placebo twice daily. The primary efficacy endpoints were mean change from baseline of FEV₁ and mean change from baseline in 12-hour FEV₁. The results were similar in the budesonide/formoterol and the budesonide + formoterol groups in all measures. The budesonide/formoterol group showed greater improvement in FEV₁ ($p \leq 0.049$) than the individual budesonide, formoterol, and placebo. Also, fewer patients on budesonide/formoterol experienced worsening asthma symptoms ($p \leq 0.025$). All of the treatments were well tolerated with similar safety profiles.

A 12-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter trial of 596 adult patients (ages 12 and older) with moderate to severe persistent asthma was conducted to evaluate patient reported outcomes (PROs) related to asthma therapy.¹⁵¹ Patients received budesonide 160 mcg twice daily for the first 2 weeks. They were then randomized to receive 2 inhalations twice daily of 1 of 5 treatment arms: budesonide/formoterol 160/4.5 mcg; budesonide 160 mcg plus formoterol DPI 4.5 mcg; budesonide 160 mcg; formoterol DPI 4.5 mcg; or placebo. PROs were assessed in 553 patients 18 years or older using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]), Medical Outcomes Survey (MOS) Sleep Scale, Patient Satisfaction with Asthma Medication (PSAM) questionnaire, diary data, and global assessments. Patients receiving budesonide/formoterol reported significantly greater improvements from baseline on the AQLQ(S) and asthma control variables (based on symptoms and rescue medication use; all $p < 0.001$) versus placebo. Clinically important improvements (increase of ≥ 0.5 points) from baseline to end of treatment in AQLQ(S) overall scores were achieved by 43.6% of patients receiving budesonide/formoterol versus 22.6% of patients receiving placebo ($p = 0.001$). The MOS Sleep Scale scores generally showed no differences among treatment groups. Patients receiving budesonide/formoterol had significantly greater PSAM questionnaire scores and better outcomes on physician-patient global assessments at end of treatment versus placebo (all $p \leq 0.001$).

budesonide/formoterol MDI (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus placebo

A 12-week, multicenter, double-blind, randomized, placebo-controlled, double-dummy study was conducted in 480 patients age 12 years or older with mild to moderate persistent asthma treated with ICS for 4 weeks or more and with an FEV₁ of 60% to 90%.¹⁵² After a 2-week washout period, patients received either budesonide/formoterol 80/4.5 mcg twice daily ($n = 123$), budesonide 80 mcg twice daily ($n = 121$), formoterol 4.5 mcg twice daily ($n = 114$), or placebo ($n = 122$). At the end of treatment, greater increases in FEV₁ occurred in the budesonide/formoterol group versus all of the other groups (0.37 versus 0.23, 0.17, and 0.03 L, respectively; $p < 0.005$). Fewer patients receiving budesonide/formoterol withdrew due to worsening asthma versus the formoterol (42.1% and 18.4%) and placebo (56.6% versus 32.8%) groups. However, the results were similar, according to the authors, with respect to worsening asthma between the budesonide/formoterol and budesonide groups (21.5% versus 6.6%).

The authors determined that in adults and adolescents with mild to moderate persistent asthma that twice daily budesonide/formoterol resulted in improved pulmonary function versus its component ingredients alone. All of the study drugs were well tolerated.

flunisolide MDI (Aerospan) versus placebo

Two double-blind, parallel, placebo- and active-controlled studies evaluated patients with asthma. The primary endpoint was change from baseline in percent predicted FEV₁ after 12 weeks of treatment.¹⁵³ Patients (N=669) aged at least 12 years old who were previously treated with ICS were randomized to flunisolide (Aerospan) MDI (80 mcg, 160 mcg, or 320 mcg) twice daily, flunisolide chlorofluorocarbon (CFC) (250 mcg, 500 mcg, or 1,000 mcg) twice daily, or placebo. Compared to placebo, the primary endpoint was statistically significant for flunisolide MDI 160 mcg (p=0.012) and 320 mcg (p=0.003) doses, but not for the 80 mcg dose.¹⁵⁴ Patients 4 to 11 years of age (n=583) who were previously treated with bronchodilators alone or ICS were randomized to flunisolide MDI (80 mcg or 160 mcg) twice daily, flunisolide CFC (250 mcg or 500 mcg) twice daily, or placebo. Primary efficacy was only evaluated for patients 6 to 11 year old. Compared to placebo, the primary endpoint was statistically significant for flunisolide MDI 80 mcg (p=0.032) and 160 mcg doses (p=0.010).

fluticasone propionate (Flovent) versus fluticasone propionate/salmeterol (Advair)

A 1-year, randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma compared fluticasone propionate and fluticasone propionate/salmeterol in achieving guideline-based measures of control: totally and well-controlled asthma.¹⁵⁵ Treatment was stepped-up until total control was achieved (or maximum 500 mcg corticosteroid twice a day). Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with fluticasone propionate/salmeterol than fluticasone propionate. Total control was achieved across all strata in 31% versus 19% of patients after dose escalation (p<0.001) and 41% versus 28% of patients at 1 year for fluticasone propionate/salmeterol and fluticasone propionate, respectively. Asthma became well controlled in 63% versus 50% after dose escalation (p<0.001) and in 71% versus 59% of patients at 1 year. Control was achieved more rapidly and at a lower corticosteroid dose with fluticasone propionate/salmeterol versus fluticasone propionate. Across all strata, 68% and 76% of the patients receiving fluticasone propionate/salmeterol and fluticasone propionate, respectively, were on the highest dose at the end of treatment. Exacerbation rates (0.07 to 0.27 per patient per year) and improvement in health status were significantly better with fluticasone propionate/salmeterol.

A multicenter, randomized, double-blind, 4-week, parallel group trial of 248 pediatric patients (ages 4 to 17 years old) with persistent asthma was conducted to evaluate the effectiveness of fluticasone propionate/salmeterol 100/50 mcg compared to fluticasone propionate 100 mcg for the prevention of airflow limitation triggered by standardized exercise challenge.¹⁵⁶ Exercise challenge tests were performed during screening and approximately 8 hours after administration of the blinded study medication on treatment day 28. After 4 weeks of therapy, both treatments provided protection following exercise challenge. The protection estimated by the maximal fall in FEV₁ was significantly better for fluticasone propionate/salmeterol (9.5 +/- 0.8%) compared with fluticasone propionate alone (12.7 +/- 1.1%, p=0.021). Statistically significant differences were not observed for asthma rescue-free days and asthma symptom-free days.

A multicenter, randomized, parallel-group, double-blind study was performed comparing fluticasone/salmeterol 50/100 mcg twice a day and fluticasone propionate 200 mcg twice a day during

a 26 week period to evaluate if the combination is non-inferior regarding symptom control and the effects on asthma control and lung function in children with symptomatic asthma.¹⁵⁷ For children with symptomatic asthma despite low to moderate doses of ICS, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of ICS. A total of 158 children age 6 to 16 years old, still symptomatic on fluticasone 100 mcg twice daily, were included in a 4-week run-in period. The percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference 2.6%; 95% CI, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percentage points in symptom-free days (both $p < 0.001$ from baseline). Lung function measurements (FEV₁, forced vital capacity [FVC], PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the fluticasone propionate/salmeterol group at 1 week. No differences were found between fluticasone propionate and fluticasone propionate/salmeterol regarding exacerbation rates, adverse events, or growth.

fluticasone propionate DPI (Flovent Diskus) versus salmeterol DPI (Serevent) versus fluticasone propionate/salmeterol DPI (Advair)

A 12-week, randomized, double-blind study was conducted in patients 12 years and older ($n=267$) with persistent asthma who were symptomatic while taking as-needed, short-acting beta₂-agonists (SABA) alone.¹⁵⁸ Treatments were administered twice daily via the fluticasone propionate/salmeterol diskus device: salmeterol 50 mcg; low-dose fluticasone propionate 100 mcg; or fluticasone propionate 100 mcg with salmeterol 50 mcg. At endpoint, fluticasone propionate/salmeterol were significantly ($p \leq 0.02$) more effective than the individual agents used alone in improving morning and evening PEF rate and asthma symptoms. In addition, fluticasone and salmeterol effectively reduced rescue albuterol use ($p \leq 0.04$).

fluticasone propionate/salmeterol DPI (Advair) versus budesonide/formoterol MDI (Symbicort)

A multicenter, parallel group, double-blind, double-dummy, randomized 24-week study was designed to compare the efficacy of salmeterol/fluticasone propionate combination 50/250 mcg 1 inhalation twice daily with formoterol/budesonide combination 6/200 mcg 2 inhalations twice daily in patients ($n=1,391$) with persistent asthma, currently receiving 1,000 to 2,000 mcg/day of ICS.¹⁵⁹ The primary endpoint, mean rate of all exacerbations over 24 weeks, was similar in both treatment groups ($p=0.571$). A reduction in the rate of exacerbations over time was observed in both treatment groups. Overall, there was a 30% lower annual rate of moderate/severe exacerbations in the salmeterol/fluticasone propionate group compared with the formoterol/budesonide group (95% CI, 0 to 49; 52% reduction versus 1% increase; $p=0.059$). Similar improvements in lung function, asthma symptoms, and rescue medication usage were seen with both treatments and both were well tolerated.

fluticasone/salmeterol (Advair Diskus) versus fluticasone (Flovent Diskus)

AUSTRI trial: A multinational, multicenter, randomized, double-blind trial in adults and adolescents (≥ 12 years old) with persistent asthma compared fluticasone/salmeterol to fluticasone alone for 26 weeks ($n=11,679$).¹⁶⁰ Patients were randomized 1:1: to fluticasone/salmeterol (100/50, 250/50, or 500/50 mcg) or fluticasone (100, 250, or 500 mcg) administered twice daily. Rescue medication was allowed. Fluticasone/salmeterol was determined to be non-inferior to fluticasone in serious asthma-related events, the primary outcome (hazard ratio [HR], 1.03; 95% CI, 0.64 to 1.66; $p=0.003$ for noninferiority).

The risk for asthma exacerbation was lower in the fluticasone/salmeterol group than the fluticasone only group (HR, 0.79; 95% CI, 0.7 to 0.89; $p<0.001$).

mometasone furoate DPI (Asmanex Twisthaler) versus budesonide DPI (Pulmicort) versus placebo

An 8-week, multicenter, placebo-controlled, double-blind, double-dummy study was conducted in 262 patients (12 years of age or older) with moderate persistent asthma to compare the safety and efficacy of once daily mometasone DPI to budesonide DPI and placebo.¹⁶¹ Patients were randomized to once daily morning treatment with mometasone 440 mcg, low-dose budesonide 400 mcg, or placebo. The primary efficacy endpoint was percent change in FEV₁ from baseline to the final evaluable visit. At endpoint, the FEV₁ was significantly greater ($p<0.01$) in the mometasone group (8.9%) than both the budesonide group (2.1%) and placebo group (-3.9%). Secondary efficacy variables including morning and evening PEF rates, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were also significantly improved at endpoint in the mometasone group compared with both the placebo and budesonide groups ($p<0.05$). Both active treatments were well tolerated.

mometasone/formoterol MDI (Dulera) versus mometasone (Asmanex HFA) versus formoterol (Foradil) versus placebo

A 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older with persistent asthma that were not well controlled on medium doses of ICS.¹⁶² The study compared mometasone/formoterol MDI 100/5 mcg, mometasone furoate MDI 100 mcg, formoterol fumarate MDI 5 mcg and placebo; each administered as 2 inhalations twice daily. All other maintenance therapies were discontinued. The FEV_{1AUC} (0-12hr) was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component. Patients receiving the combination mometasone/formoterol had significantly higher increases from baseline at week 12 in mean FEV_{1AUC} (0-12 hr) compared to mometasone furoate and placebo (both $p<0.001$). These differences were maintained through week 26. Clinical deterioration in asthma or reductions in lung function was another primary endpoint to evaluate the contribution of mometasone furoate. Deteriorations in asthma were defined as any of the following: a 20% decrease in FEV₁; a 30% decrease in PEF on 2 or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Fewer patients who received the combination mometasone/formoterol (30%) reported an event compared to patients who received formoterol (54%) ($p<0.001$).

mometasone/formoterol MDI (Dulera) versus mometasone (Asmanex HFA) versus formoterol (Foradil) versus placebo

A 12-week double-blind trial evaluated 728 patients ages 12 years and older with persistent asthma that were uncontrolled on high dose ICS.¹⁶³ This study compared mometasone/formoterol 200/5 mcg with mometasone/formoterol 100/5 mcg and mometasone furoate 200 mcg, each administered as 2 inhalations twice daily by MDIs. All other maintenance therapies were discontinued. Patients receiving either mometasone/formoterol dosages had significantly greater increases from baseline at day 1 in mean FEV_{1AUC} (0-12 hr) compared to mometasone furoate. The difference was maintained over 12 weeks of therapy. Mean change in trough FEV₁ from baseline to week 12 was also assessed to evaluate the relative contribution of mometasone furoate to the combination product. A greater numerical increase in the mean trough FEV₁ was observed for the higher strength mometasone/formoterol compared to

the lower strength mometasone/formoterol and mometasone monotherapy. Clinical deterioration in asthma or reduction in lung function was assessed as an additional endpoint. Fewer patients who received either strength mometasone/formoterol (12% for each group) compared to mometasone furoate (18%) alone reported an event.

ciclesonide MDI (Alvesco) versus budesonide DPI (Pulmicort)

A 12-week, multicenter, randomized study to compare the efficacy of ciclesonide to budesonide enrolled 544 patients ages 12 to 75 years.¹⁶⁴ Patients were randomized to receive inhaled ciclesonide 80 or 320 mcg daily or budesonide 200 mcg twice daily for 12 weeks. The study was designed in a double-blind manner with respect to the ciclesonide dose and open-label for budesonide because a placebo for budesonide was not available. Efficacy and tolerability assessments were performed at baseline and weeks 4, 8, and 12. The primary endpoint was the change from baseline in FEV₁ at 12 weeks. Secondary endpoints included changes from baseline in morning PEF, asthma symptom scores, and rescue medication use. The results of this study in patients with primarily mild to moderate asthma suggest that patients using either dose of ciclesonide (80 or 320 mcg daily) had similar improvements in pulmonary function, control of asthma symptoms, and reduced need for rescue medications as those patients who received budesonide 200 mcg twice daily.

ciclesonide MDI (Alvesco) versus fluticasone (Flovent)

A 12-week, double-blind, parallel-group study compared the efficacy and safety of once daily ciclesonide and twice daily fluticasone in patients ages 12 to 75 years with persistent asthma.¹⁶⁵ Patients were randomized to once daily ciclesonide 80 mcg (n=278), ciclesonide 160 mcg (n=271), or twice daily fluticasone 88 mcg (n=259). Significant improvements from baseline were seen in all 3 treatment groups for FEV₁, asthma symptom scores, and rescue medication use (all p<0.0001). Asthma exacerbation rates were low. Adverse event reporting indicated good tolerability of all treatments.

fluticasone furoate (Arnuity Ellipta) versus fluticasone propionate (Flovent Diskus)

This randomized, double-blind, double-dummy, placebo-controlled, multicenter study, enrolled 343 patients with asthma, aged 12 years or older who were not controlled by their current ICS therapy.¹⁶⁶ The primary endpoint was change from baseline in pre-dose evening FEV₁ at the end of the 24-week treatment period. Patients randomly received fluticasone furoate (100 mcg) once daily, placebo once daily, or twice daily administered fluticasone propionate (250 mcg). At week 24, once daily fluticasone furoate and twice daily fluticasone propionate significantly improved pre-dose evening FEV₁ (+146 mL; p=0.009) compared with placebo (+145 mL; p=0.011). The secondary endpoint of percentage rescue-free 24-hour periods, was increased with fluticasone furoate (+14.8%; p<0.001) and fluticasone propionate (+17.9%; p<0.001) compared to placebo.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone furoate (Arnuity Ellipta)

In two, 12-week randomized, double-blind, parallel-group trials, the efficacy of fluticasone furoate/vilanterol on lung function was compared to fluticasone furoate alone in subjects with asthma not controlled on their current treatments of ICS or ICS/LABA.¹⁶⁷ In both studies, all inhalations were administered once daily. In study 1, 609 patients were randomized to fluticasone furoate/vilanterol 100/25 mcg, fluticasone furoate 100 mcg, or placebo. Weighted mean FEV₁ (0 to 24 hours) was assessed in a subset of subjects (n=309). At week 12, change from baseline in weighted mean FEV₁ was significantly greater for fluticasone furoate/vilanterol 100/25 mcg compared with placebo (302 mL; 95% CI, 178 to 426; p<0.001); change from baseline in weighted mean FEV₁ for fluticasone

furoate/vilanterol 100/25 was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (116 mL; 95% CI, -5 to 236). At week 12, change from baseline in trough FEV₁ was significantly greater for fluticasone furoate/vilanterol 100/25 compared with placebo (172 mL; 95% CI, 87 to 258; p<0.001); change from baseline in trough FEV₁ for fluticasone furoate/vilanterol 100/25 mcg was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (36 mL; 95% CI, -48 to 120). In study 2, 1,039 patients were randomized to fluticasone furoate/vilanterol 100/25 mcg, fluticasone furoate/vilanterol 200/25 mcg, or fluticasone furoate 100 mcg.^{168,169} The change from baseline in weighted mean FEV₁ (0 to 24 hours) was significantly greater for fluticasone furoate/vilanterol 100/25 mcg compared with fluticasone furoate 100 mcg (108 mL; 95% CI, 45 to 171; p<0.001) at week 12. Improvements in FEV₁ were numerically greater with fluticasone furoate/vilanterol 200/25 mcg compared to the 100/25 mcg dose but these differences were not statistically significant.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate (Flovent Diskus)

In a 24-week randomized, double-blind, parallel-group trial, patients (n=586) not controlled on their current treatments of ICS or combination therapy consisting of an ICS plus a LABA were randomized to fluticasone furoate/vilanterol 200/25 mcg, fluticasone furoate 200 mcg, or fluticasone propionate 500 mcg.¹⁷⁰ All inhalations were administered once daily, with the exception of fluticasone propionate, which was administered twice daily. The change from baseline in weighted mean FEV₁ (0 to 24 hours) was significantly greater for fluticasone furoate/vilanterol 200/25 mcg compared with fluticasone furoate 200 mcg (136 mL; 95% CI, 1 to 270; p=0.048) at week 24. The change from baseline in trough FEV₁ was significantly greater for fluticasone furoate/vilanterol 200/25 mcg compared with fluticasone furoate 200 mcg (193 mL; 95% CI, 108 to 277; p<0.001) at week 24. Patients receiving fluticasone furoate/vilanterol 200/25 mcg had significantly greater improvements from baseline in percentage of 24-hour periods without need of beta₂-agonist rescue medication use and percentage of 24-hour periods without asthma symptoms compared with patients receiving fluticasone furoate 200 mcg.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate/salmeterol (Advair)

In a randomized, double-blind, double-dummy, parallel group study, 403 patients received fluticasone furoate/vilanterol 100/25 mcg once daily in the evening, and 403 patients received fluticasone propionate/salmeterol 250/50 mcg twice daily.¹⁷¹ Improvements from baseline in weighted mean FEV₁ (0 to 24 hours) were observed with both fluticasone furoate/vilanterol (341 mL) and fluticasone propionate/salmeterol (377 mL); the adjusted mean treatment difference was not statistically significant (-37 mL; 95% CI, -88 to 15, p=0.162). There were no differences between 0 to 4 hour serial weighted mean FEV₁, trough FEV₁, asthma control and quality-of-life questionnaire scores, and reported exacerbations between treatments.

COPD

budesonide/formoterol (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus placebo

In a 12-month, randomized, double-blind, placebo-controlled, parallel-group study in 812 adults (mean age 64 years, mean FEV₁ 36%), patients with moderate to severe COPD received 2 inhalations twice daily of either budesonide/formoterol 160/4.5 mcg, budesonide 200 mcg, formoterol 4.5 mcg, or placebo.¹⁷² Severe exacerbations and FEV₁ were the primary variables. Other variables including PEF, COPD symptoms, health-related quality of life (HRQL), mild exacerbations, use of reliever beta₂-

agonist, and safety variables were recorded. Budesonide/formoterol reduced the mean number of severe exacerbations per patient per year by 24% versus placebo and 23% versus formoterol. For patients receiving budesonide/formoterol, FEV₁ increased by 15% versus placebo and 9% versus budesonide. Morning PEF improved significantly on day 1 versus placebo and budesonide. After 1 week, morning PEF was improved versus placebo, budesonide, and formoterol. Improvements in morning and evening PEF versus comparators were maintained over 12 months. Budesonide/formoterol decreased all symptom scores and use of reliever beta₂-agonists significantly versus placebo and budesonide, and improved HRQL versus placebo. All treatments were well tolerated.

The SHINE trial was a 6-month, double-blind, multicenter trial that evaluated the efficacy and tolerability of budesonide/formoterol in 1,704 patients ages 40 years and older with moderate to very severe COPD.¹⁷³ Patients were randomized to receive twice daily treatment with 2 inhalations of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg, budesonide 160 mcg + formoterol 4.5 mcg, budesonide 160 mcg, formoterol 4.5 mcg, or placebo. Primary outcomes measures included pre-dose and 1-hour post-dose FEV₁ over the 6 month treatment period. Budesonide/formoterol 160/4.5 mcg twice a day (320/9 mcg) improved both pre-dose and 1-hour post-dose FEV₁ compared to either of the components alone or to placebo ($p \leq 0.039$ for all). At the lower dose of 80/4.5 mcg twice a day (160/9 mcg), there was significantly greater improvement in pre-dose FEV₁ and 1-hour post-dose FEV₁ compared with budesonide and placebo ($p \leq 0.002$ for all), but not compared to formoterol. Budesonide/formoterol had a safety profile comparable with that of the mono components and placebo.

budesonide/formoterol (Symbicort) versus fluticasone propionate/salmeterol (Advair) versus salbutamol versus placebo

In a double-blind, double-dummy, crossover study, 90 patients (age 40 years and older; FEV₁ 30% to 70%) were randomized to a single dose (2 inhalations) of budesonide/formoterol 160/4.5 mcg, fluticasone propionate/salmeterol 250/25 mcg, salbutamol 100 mcg, or placebo on 4 visits.¹⁷⁴ Outside the United States albuterol is known as salbutamol. The primary endpoint was change in FEV₁ 5 minutes after drug inhalation; secondary endpoints included inspiratory capacity (IC) and perception of onset of effect. Budesonide/formoterol significantly improved FEV₁ at 5 minutes compared with placebo ($p < 0.0001$) and fluticasone propionate/salmeterol ($p = 0.0001$). Significant differences were first observed at 3 minutes. Onset of effect was similar with budesonide/formoterol and salbutamol. Improvements in FEV₁ following active treatments were superior to placebo after 180 minutes (all $p < 0.0001$); both combinations were better than salbutamol at maintaining FEV₁ improvements ($p \leq 0.0001$) at 180 minutes. Active treatments improved IC at 15 and 185 minutes compared with placebo ($p < 0.0001$). Maximal IC was greater with budesonide/formoterol than fluticasone propionate/salmeterol ($p = 0.0184$) at 65 minutes. Patients reported a positive response to the perceptions of the onset of effect question shortly after receiving active treatments (median time to onset was 5 minutes for active treatments versus 20 minutes for placebo), with no significant difference between active treatments. Budesonide/formoterol has an onset of bronchodilatory effect in patients with COPD and reversible airway obstruction that is faster than fluticasone propionate/salmeterol and similar to salbutamol.

fluticasone propionate DPI (Flovent) versus salmeterol DPI (Serevent) versus fluticasone propionate/salmeterol DPI (Advair)

In a double-blind, parallel-group, placebo-controlled study, 1,465 patients with COPD were randomized to receive salmeterol 50 mcg twice daily, high-dose fluticasone 500 mcg twice daily, fluticasone propionate/salmeterol 500/50 mcg twice daily, or placebo.¹⁷⁵ After 12 months, all active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV₁ significantly more than did placebo (treatment difference 133 mL; 95% CI, 105 to 161; p<0.0001), salmeterol (73 mL; 95% CI, 46 to 101; p<0.0001), or fluticasone alone (95 mL; 95% CI, 67 to 122; p<0.0001). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

In 2 randomized, double-blind, parallel-group, multinational, 1-year trials, a total of 3,255 COPD patients with a history of exacerbations received once daily treatment with vilanterol alone or combined with various doses of fluticasone furoate.¹⁷⁶ Results from these studies are presented individually and in a pooled analysis. Patients ≥ 40 years of age, with COPD and a history of smoking of 10 or more pack-years, a ratio FEV₁ to FVC of ≤ 0.70 after bronchodilators (and an FEV₁ of ≤ 70% of predicted) and a documented history of at least 1 exacerbation in the previous year were eligible. Study 1 enrolled 1,622 patients; study 2 enrolled 1,633 patients. After a 4-week run-in period of treatment with open-label fluticasone propionate (250 mcg)/salmeterol (50 mcg) twice daily to establish a stable baseline and adherence, patients were randomized 1:1:1:1 to 25 mcg vilanterol alone or 25 mcg vilanterol combined with either 50 mcg, 100 mcg, or 200 mcg fluticasone furoate once daily in the morning. The primary outcome measure was the yearly rate of moderate and severe exacerbations. Moderate exacerbation was defined as worsening symptoms for ≥ 2 days requiring treatment with oral corticosteroids, antibiotics or both. Severe exacerbations were similar but patients required hospitalization. In Study 1, the difference in yearly rate of exacerbations between the fluticasone furoate/vilanterol 200/25 mcg group and the vilanterol alone group did not reach significance (least squares mean yearly rate 0.9 fluticasone/vilanterol versus 1.05 vilanterol; p=0.1093). The study design employed a statistical hierarchical testing procedure so comparisons of other dosage groups could not be used to infer significance. In Study 2, the differences in yearly rate of exacerbations between all fluticasone furoate/vilanterol groups and the vilanterol alone group were significant. In the 100 mcg fluticasone furoate/25 mcg vilanterol group (approved dose), the least squares mean yearly rate was 0.9 compared to 1.14 in the vilanterol alone group (p=0.0244). In the pooled analysis, the difference between all doses of fluticasone furoate/vilanterol and vilanterol alone was significant and the combination of fluticasone 100 mcg and vilanterol 25 mcg significantly reduced the yearly rate of moderate and severe exacerbations compared to vilanterol alone (0.81 versus 1.11). In these trials, the difference in exacerbation rate was driven primarily in a reduction in moderate exacerbations; few severe exacerbations occurred and the difference between groups in severe exacerbation rate was not significant. The incidence of fractures and pneumonia was higher with fluticasone furoate/vilanterol than with vilanterol alone. Fractures were reported in 19 (100 mcg fluticasone furoate/25 mcg vilanterol) patients compared to 8 vilanterol patients. Overall, pneumonia occurred at about twice the rate in the fluticasone furoate/vilanterol groups compared to the vilanterol group (100 mcg fluticasone furoate/25 mcg vilanterol: 51 events versus 25 mcg vilanterol: 27 events). One case of pneumonia in the group receiving fluticasone furoate/vilanterol 100/25 mcg and 7

cases of pneumonia in the group receiving fluticasone furoate/vilanterol 200/25 mcg were fatal compared to none in the vilanterol or fluticasone furoate monotherapy groups.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone furoate (Advair Diskus) and vilanterol

SUMMIT: A multicenter, multinational, randomized, double-blind trial compared the efficacy of fluticasone furoate/vilanterol 100/25 mcg to fluticasone furoate 100 mcg and vilanterol 25 mcg alone in 16,590 adults with COPD (FEV₁ 50% to 70% predicted).¹⁷⁷ All-cause mortality, the primary outcome, was not statistically different when each component was compared to placebo (HR, 0.88 [95% CI, 0.74 to 1.04]; HR, 0.91 [95% CI, 0.77 to 1.08]; and HR, 0.96 [95% CI, 0.81 to 1.14] for the combination, fluticasone only, and vilanterol only, respectively). Likewise, no difference was found in the composite of cardiovascular events. However, all active treatment groups reduced the rate of moderate and severe exacerbations. The on-treatment rate of FEV₁ decline was 46 mL/year with placebo, 38 mL/year with fluticasone furoate (difference versus placebo, 8 mL; 95% CI, 1 to 14), 47 mL/year with vilanterol (difference versus placebo, -2 mL; 95% CI, -8 to 5), and 38 mL/year with the combination (difference versus placebo, 8 mL; 95% CI, 1 to 15).

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate/salmeterol (Advair Diskus)

Three randomized, double-blind, double-dummy, parallel-group, comparative multicenter studies compared the efficacy and safety of fluticasone furoate/vilanterol 100/25 mcg once daily, or fluticasone propionate/salmeterol 250/50 mcg twice daily for 12 weeks in 1,858 patients with moderate to very severe COPD.¹⁷⁸ The primary endpoint of each study was change from baseline trough in 0–24 hour weighted mean FEV₁ (wmFEV₁) on day 84, using intent-to-treat population. Improvements in 0–24 hour wmFEV₁ were seen with both fluticasone furoate/vilanterol 100/25 mcg and fluticasone propionate/salmeterol 250/50 mcg compared with baseline trough in all 3 studies and in the pooled analysis. In study 1, the treatment difference between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol was statistically significant (80 mL, p<0.001); however, in studies 2 and 3, the difference was not statistically or clinically significant (29 mL p=0.267; 25 mL, p=0.137, respectively). In the pooled analysis of all 3 studies, there was a small statistically significant but clinically insignificant treatment difference of 41 mL (p<0.001); this is below the suggested minimal clinically important difference for lung function. Both treatments were well tolerated with generally similar safety profiles.

fluticasone propionate/salmeterol (Advair) versus umeclidinium/vilanterol (Anoro Ellipta)

Two 12-week, multicenter, double-blind, parallel-group, double-dummy, randomized trials compared the efficacy of fluticasone/salmeterol to umeclidinium/vilanterol in patients with moderate to severe COPD (Study 1, n=706; Study 2, n=697).¹⁷⁹ Patients with infrequent exacerbations were randomized 1:1 to twice-daily fluticasone/salmeterol 250/50 mcg or once-daily umeclidinium/vilanterol 62.5/25 mcg. Key endpoints included 0 to 24 hour mean FEV₁ on Day 84 (primary), trough FEV₁ on day 85, dyspnea, and change in SGRQ score. Umeclidinium/vilanterol demonstrated significant improvement in lung function compared to fluticasone/salmeterol; the difference in FEV₁₍₀₋₂₄₎ on day 84 was 74 mL (95% CI, 38 to 110) in Study 1 and 101 mL (95% CI, 63 to 139 in Study 2; p<0.001 for both). Trough FEV₁ values were also superior with umeclidinium/vilanterol in both trials; however, no difference was seen between groups in dyspnea ratings or SGRQ improvement. Adverse event rates were similar between groups.

Clinical Trials: Safety

There is concern that prolonged treatment with high doses of ICS may have a detrimental effect on bone mineral density (BMD), cause ocular toxicity, suppress the adrenal/pituitary axis, and inhibit vertical growth.

budesonide (Pulmicort Respules) versus reference treatments

Pooled safety data from budesonide inhalation suspension studies (n=2,356) found there were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in 2 of 5 trials that evaluated this variable.¹⁸⁰ No posterior subcapsular cataracts were reported in any study. The frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable.

Data from the inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study evaluated the safety of once daily budesonide use over 3 years in patients aged 5 to 66 years with mild, persistent asthma (n=7,221).¹⁸¹ The most commonly reported events included respiratory infections, rhinitis, pharyngitis, bronchitis, viral infections, and sinusitis. Fewer asthma-related, serious adverse events were reported with budesonide (2.2%) compared with placebo (3.8%). Oral candidiasis was reported more frequently with budesonide (1.2%) than with placebo (0.5%).

A further analysis of the START trial was conducted to determine whether severe asthma exacerbations are associated with a persistent decline in lung function.¹⁸² This study was a 3-year, randomized, double-blind trial that enrolled 7,165 patients (5 to 66 years of age) with persistent asthma. There were 315 patients who experienced at least 1 severe asthma exacerbation, of which 305 were analyzable, 190 in the placebo group and 115 in the budesonide group. In the placebo group, the change in post-bronchodilator FEV₁ percent predicted from baseline to the end of the study, in patients who did or did not experience a severe exacerbation was -6.44% and -2.43%, respectively (p<0.001). A significant difference was seen in both children and in adults, but not in adolescents. In the budesonide group, the change in the post-bronchodilator FEV₁ percent predicted in patients who did or did not experience a severe exacerbation was -2.48% and -1.72%, respectively (p=0.57). The difference in magnitude of reduction afforded by budesonide, in patients who experienced at least 1 severe asthma-related event compared with those who did not, was statistically significant (p=0.042). Severe asthma exacerbations are associated with a more rapid decline in lung function. Treatment with low doses of ICS is associated with an attenuation of the decline.

fluticasone propionate MDI (Flovent) versus budesonide MDI (Pulmicort)

Forty children (age 1 to 3 years) with mild asthma were studied in a 3-way crossover, randomized, placebo-controlled, double-blind trial.¹⁸³ Treatment with medium-dose fluticasone MDI 200 mcg twice daily was compared with low-dose budesonide MDI 200 mcg twice daily and placebo, all given via a spacer device. Systemic steroid activity was assessed after 1 and 4 weeks of treatment by measured increase in lower-leg length. The increases in lower-leg length during placebo, budesonide, and fluticasone treatments were 85, 45, and 34 mcm/day, respectively. Compared to placebo, the growth in lower-leg length was significantly reduced from both corticosteroid treatments. The differences between budesonide and placebo (40 mcm/day) and between fluticasone and placebo (51 mcm/day)

were statistically significant. The difference between the 2 active treatment groups, fluticasone and budesonide, was not statistically significant.

fluticasone propionate/salmeterol DPI (Advair) and fluticasone propionate DPI (Flovent)

A randomized, multicenter, double-blind, active-controlled, parallel-group study in 203 children with persistent asthma who were symptomatic during ICS therapy were examined to compare the safety of twice daily treatment of inhaled fluticasone/salmeterol with that of fluticasone alone.¹⁸⁴ The subjects received either fluticasone/salmeterol (100/50 mcg) or low-dose fluticasone (100 mcg) alone twice daily for 12 weeks. The results of the study showed that the safety profile of fluticasone/salmeterol was comparable to that of fluticasone alone with the overall incidence of adverse events being 59% for fluticasone/salmeterol and 57% for fluticasone. The changes in heart rate, blood pressure, and laboratory variables were infrequent and similar between both groups, and no patients had clinically significant abnormal electrocardiographic findings during treatment. The incidence of withdrawals within the study due to asthma exacerbations was 2% in the fluticasone/salmeterol group and 5% in the fluticasone group. Therefore, the study concluded that in children with persistent asthma, fluticasone/salmeterol twice daily was well tolerated, with a safety profile similar to that of fluticasone used alone.

budesonide DPI (Pulmicort) versus fluticasone propionate DPI (Flovent)

The systemic effects of high-dose budesonide 1,600 mcg/day and high-dose fluticasone 1,500 mcg/day were compared in a randomized, double-blind, cross-over study of 60 adult patients with moderate to severe asthma not controlled on high-dose beclomethasone or budesonide.¹⁸⁵ HPA axis suppression of the 2 treatment groups was assessed by morning serum cortisol and 12-hour nocturnal urinary cortisol excretion measured at the end of each treatment period. Neither treatment produced significant suppression of either parameter compared to baselines. The ratio between the AUC serum cortisol measured after fluticasone treatment and after budesonide treatment was 0.99, indicating equivalent effects on the HPA axis. Two exacerbations of acute asthma occurred during budesonide treatment, and none occurred during fluticasone treatment. Both treatments were well tolerated.

Bone Mineral Density and Fracture

Several studies have been performed to evaluate the relative effects of the various agents on bone mass and metabolism.

A multicenter, double-blind, parallel-group study randomized 69 adults with mild to moderate asthma to treatment with medium or high doses of fluticasone propionate or beclomethasone.¹⁸⁶ After 1 year, there was no loss of trabecular or integral bone in the distal radius or tibia in any of the patients.

However, a meta-analysis of included randomized controlled trials (16 trials; n=17,513) of budesonide or fluticasone propionate compared to control treatment for COPD greater than 24 weeks duration and controlled observational studies (7 studies; n=69,000) of ICS associated fracture risk.¹⁸⁷ This study reported a modest but statistically significant increase in risk of fracture with long-term use of fluticasone propionate and budesonide.

Linear Growth

Orally ICS may cause a reduction in growth velocity when administered to children and adolescents.¹⁸⁸ A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids.

Evidence on growth velocity and height over an extended time period is available from the Childhood Asthma Management Program (CAMP) trial that compared budesonide with nedocromil and placebo in 1,041 children followed for 4 to 6 years.¹⁸⁹ A difference consistent with the above magnitude occurred during the first year of the study. However, in long-term follow up, the difference in growth velocity was not maintained, and all groups had similar growth velocity at the end of treatment. There was still a 1 centimeter difference between the study groups at the end of treatment. A slight difference in bone age suggests the potential for catch-up for the ICS group. A follow-on study with 943 of the original 1,041 children showed a statistically significant reduction of 1.2 cm in mean adult height (95% CI, -1.9 to -0.5) for the budesonide arm as compared to the placebo group ($p=0.001$).¹⁹⁰ This magnitude height difference is consistent with the results seen after 2 years of treatment (-1.3 cm; 95% CI, -1.7 cm to -0.9 cm).¹⁹¹

An ancillary study of the CAMP trial demonstrated that low-dose budesonide 400 mcg/day over a 3-year period had no effects on HPA axis function in children with mild to moderate asthma.¹⁹² Growth in children taking corticosteroids by any route should be carefully monitored.

META-ANALYSES

In 2007, a meta-analysis was completed of randomized trials in children and adults comparing fluticasone to either beclomethasone or budesonide in the treatment of chronic asthma.¹⁹³ Two reviewers independently assessed articles for inclusion and methodological quality. Seventy-one studies (14,602 participants) representing 74 randomized comparisons met the inclusion criteria. When compared at a fluticasone-to-budesonide or beclomethasone dose ratio of 1:2, fluticasone produced an end of treatment FEV₁ that was not statistically different from budesonide or beclomethasone (change in FEV₁, 0.04 L; 95% CI, 0 to 0.07). There was also a lack of a statistical difference in change from baseline in FEV₁ between the treatment groups (change in FEV₁, 0.01 L; 95% CI, -0.02 to 0.04). In contrast the mean difference in change in morning peak expiratory flow (PEF) from baseline at the end of treatment was statistically significant (change in morning PEF, 7.42 L/min; 95% CI, 4.97 to 9.87). However, there was no significant difference in change in evening PEF. This applied to all drug doses, age groups, and delivery devices. No difference between fluticasone and beclomethasone or budesonide was seen for trial withdrawals. Fluticasone led to fewer symptoms and less rescue medication use. There was a greater likelihood of pharyngitis with fluticasone when compared to budesonide or beclomethasone with no difference in the likelihood of oral candidiasis. Comparing these agents in a dose ratio of 1:1, fluticasone produced a statistically significant difference in end of treatment FEV₁ over both budesonide and beclomethasone (change in FEV₁, 0.04 L; 95% CI, 0.01 to 0.07). Although the change from baseline was not significantly different between the treatments (change in FEV₁, 0.01 L; 95% CI, -0.03 to 0.05). There were also significant mean differences in absolute morning and evening PEFs between treatments and the change from baseline in morning PEF but not for the change from baseline in evening PEF between the treatment groups. The effects on exacerbations were mixed. There were no significant differences in the incidence of hoarseness, pharyngitis, candidiasis, or cough at the equivalent dose ratio.

A meta-analysis of published and unpublished literature evaluated the impact of long-term inhaled corticosteroid use on bone density in adult patients with asthma or COPD.¹⁹⁴ The authors found that long-term use was not associated with significant changes in bone density.

In 2010, a meta-analysis of randomized, controlled trials (RCTs) that compared the strategy of increasing the daily dose of ICS to continuing the same ICS dose in the home management of asthma

exacerbations in children or adults with persistent asthma who receive daily maintenance ICS.¹⁹⁵ Five RCTs (4 parallel-group and 1 cross-over) involving a total of 1,250 patients (28 children and 1,222 adults) with mild to moderate asthma were included. The mean daily baseline ICS dose was 555 mcg (range 200 mcg to 795 mcg) and the mean daily ICS dose achieved following the increase was 1,520 mcg (range 1,000 mcg to 2,075 mcg), in beclomethasone dipropionate equivalents. Three parallel-group studies in adults (2 doubling and 1 quadrupling; mean achieved daily dose of 1,695 mcg with a range of 1,420 to 2,075 mcg), involving 1,080 patients contributed data to the primary outcome. There was no significant reduction in the need for rescue oral corticosteroids when patients were randomized to the increased dose of ICS compared to the stable maintenance dose groups (OR 0.85; 95% CI, 0.58 to 1.26). Statistically, there was no significant difference in the overall risk of non-serious adverse events associated with the increased ICS dose strategy, but the wide confidence interval prevents a firm conclusion. No serious adverse events were reported.

In 2011, a meta-analysis that compared 2 or more doses of ICS in pediatric patients (age 3 to 18 years) with persistent asthma was published to assess the dose-response relationship including benefits and harms of ICS in children with persistent asthma.¹⁹⁶ A Medline search was conducted for articles published between 1950 and August 2009. Main outcomes of this analysis included morning and evening PEF, FEV₁, asthma symptom score, beta₂ agonist use, withdrawal because of lack of efficacy, and adverse events. Meta-analyses were performed to compare moderate (300 to 400 mcg daily) with low (\leq 200 mcg daily beclomethasone-equivalent) doses of the ICS. Fourteen RCTs that included 5,768 asthmatic children that evaluated 5 different ICS were included in the analysis. The pooled standardized mean difference from 6 trials revealed a small but statistically significant increase of moderate over low doses in improving FEV₁ (standardized mean difference, 0.11; 95% CI, 0.01 to 0.21) among children with mild-to-moderate asthma. There was no significant difference between 2 doses in terms of other efficacy outcomes. Local adverse events were uncommon, and there was no evidence of dose-response relationship at low-to-moderate doses.

In 2011, a meta-analysis compared the relative effects of ICS compared to long-acting beta₂-agonists (LABA) on clinical outcomes in patients with stable COPD in 5,997 patients (7 RCTs).¹⁹⁷ All of the trials compared ICS/LABA combination inhalers with LABA and ICS as individual components. Four of these trials included fluticasone and salmeterol mono components and the remaining 3 included budesonide and formoterol mono components. There was no statistically significant difference in the primary outcome, the number of patients experiencing exacerbations (odds ratio (OR), 1.22; 95% CI, 0.89 to 1.67), or the rate of exacerbations per patient year (rate ratio (RR), 0.96; 95% CI, 0.89 to 1.02) between ICS and LABAs. The incidence of pneumonia, the co-primary outcome, was significantly higher among patients on ICS than on LABAs whether classified as an adverse event (OR, 1.38; 95% CI, 1.1 to 1.73) or serious adverse event (Peto OR, 1.48; 95% CI, 1.13 to 1.93). In terms of the secondary outcomes analysis, mortality was higher in patients on ICS compared to patients on LABAs (Peto OR, 1.17; 95% CI, 0.97 to 1.42), although the difference was not statistically significant. Patients treated with beta₂-agonists showed greater improvements in pre-bronchodilator FEV₁ compared to those treated with ICS (mean difference (MD), 18.99 mL; 95% CI, 0.52 to 37.46). However, there were greater improvements in health-related quality of life observed in patients receiving ICS compared to those receiving long LABAs (St George's Respiratory Questionnaire (SGRQ) MD, -0.74; 95% CI, -1.42 to -0.06). In both cases, the differences were statistically significant but rather small in magnitude. There were no statistically significant differences between ICS and LABA in the number of hospitalizations due to exacerbations, number of mild exacerbations, PEF, dyspnea, symptoms scores, use of rescue medication, adverse events, all cause hospitalizations, or withdrawals from studies. The authors concluded that their

findings support current guidelines advocating LABAs as frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations.

A Cochrane database systematic review evaluated ICS in stable COPD.¹⁹⁸ Fifty-five randomized, placebo-controlled studies, representing 16,154 patients, and 5 different ICS (budesonide, beclomethasone dipropionate, fluticasone propionate, triamcinolone acetonide, mometasone furoate) were included in the analysis. The rate of decline of FEV₁ was not blunted by the extended use (greater than 6 months) of ICS in COPD patients (generic inverse variance analysis: mean difference [MD], 5.8 mL/year with ICS over placebo [95% CI, -0.28 to 11.88; 2,333 participants]; pooled means analysis: 6.88 mL/year [95% CI 1.8 to 11.96, 4,823 participants]). However, statistically significant reductions were seen in the mean rate of exacerbations (generic inverse variance analysis: MD, -0.26 exacerbations per patient per year [95% CI -0.37 to -0.14; 2,586 participants]; pooled means analysis: MD, -0.19 exacerbations per patient per year [95% CI -0.3 to -0.08; 2,253 participants]) and the rate of decline in quality of life as measured by the St. George's Respiratory Questionnaire (MD, -1.22 units/year; 95% CI -1.83 to -0.6; 2,507 participants). Conversely, increased rates of oropharyngeal candidiasis (OR, 2.65; 95% CI, 2.03 to 3.46; 5,586 participants) and pneumonia were observed in patients utilizing ICS. No statistically significant effect on mortality was observed (OR, 0.98, 95% CI, 0.83 to 1.16; 8,390 participants). This review advises clinicians to balance the increased risk of adverse effects (e.g., oropharyngeal candidiasis and pneumonia), when considering the use of ICS in COPD to capture the potential benefits of decreased rates of exacerbations and quality of life decline.

A separate meta-analysis looked at the comparison of ICS/LABA products to LABA alone.¹⁹⁹ Fourteen randomized, blinded studies enrolling 11,794 individuals met inclusion criteria for the analysis. Risk of mortality did not differ significantly between the 2 therapies (OR, 0.92; 95% CI, 0.76 to 1.11; moderate quality). Pneumonia was more common in the ICS/LABA group as compared to LABA alone (OR, 1.55; 95% CI, 1.2 to 2.01; moderate quality). The other primary outcomes, including rate of hospitalizations and risk of exacerbation, were determined to have low quality evidence by the reviewers; neither outcome demonstrated a significant difference between the 2 groups.

SUMMARY

The 2007 National Heart, Lung, and Blood Institute (NHLBI) and 2016 Global Initiative for Asthma (GINA) guidelines both utilize a classification of level of asthma control to guide asthma therapy and state that inhaled corticosteroids (ICS) are currently the most effective anti-inflammatory medications for the treatment of persistent asthma.

Bronchodilator therapy is central to symptom management in chronic obstructive pulmonary disease and the inhaled route is preferred. The GOLD guidelines recommend the addition of ICS to long-acting bronchodilator therapy, such as long-acting beta₂-agonists, for patients with severe to very severe COPD.

When used in equivalent dosages, efficacy among all inhaled corticosteroids is similar. There are differences among the agents in dosage frequency and the number of inhalations needed for each dose. Most of these agents are recommended for twice daily use. The exceptions to this are mometasone (Asmanex Twisthaler DPI) and fluticasone furoate (Arnuity Ellipta), which can be dosed once daily. Also, there are 2 agents that act as prodrugs, ciclesonide (Alvesco) and beclomethasone (QVAR). They are both converted either during absorption (beclomethasone) or by esterases in the lung (ciclesonide).

The use of a combination long-acting beta agonist and an ICS [e.g., salmeterol/fluticasone propionate (Advair), formoterol/budesonide (Symbicort), formoterol/mometasone (Dulera), fluticasone furoate/vilanterol (Breo Ellipta)] in a single inhaler is effective in the treatment of asthma and reduces asthma exacerbations. Salmeterol/fluticasone propionate (Advair), formoterol/budesonide (Symbicort), and fluticasone furoate/vilanterol (Breo Ellipta) are also indicated for the maintenance treatment of airflow obstruction in patients with COPD; formoterol/mometasone (Dulera) is not approved for this indication. Fluticasone furoate/vilanterol (Breo Ellipta) is dosed once daily while budesonide/formoterol (Symbicort) and fluticasone propionate/salmeterol (Advair) are dosed twice daily. FDA recommendations on the safe use of long-acting beta₂-agonists in the treatment of asthma, also apply to the combination ICS/long-acting beta₂-agonist products. The FDA recommends against the use of long-acting beta₂-agonists without the use of an asthma controller medication such as an ICS. Also, long-acting beta₂-agonists should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Long-acting beta₂-agonists should be used long-term only in patients whose asthma is not adequately controlled on other asthma controller medications. When selecting an agent for an individual patient, consideration must be given to the characteristics of the particular delivery device and the necessary technique for its use. This is particularly important for the very young and the very old. For children under 5 years of age, a metered-dose inhaler (MDI) with a spacer and an optional face mask or mouthpiece may be preferable. If this is not effective, consideration could be given towards nebulizer therapy or a dry-powder inhaler (DPI) as an alternative for individuals, young and old, who cannot use MDIs due to an inability to coordinate hand and press devices.

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